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Preoperative pathologic findings associated with residual disease at radical hysterectomy in women with stage IA2 cervical cancer

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Abstract

Objective—To correlate findings on pathologic examination of loop electroexcisional procedure (LEEP) or cone biopsy specimens with residual disease in radical hysterectomy specimens in patients with stage IA2 cervical cancer to determine whether a subset of such patients may be eligible for conservative, fertility-sparing treatment.

Methods—We performed a retrospective chart review of patients diagnosed with stage IA2 cervical cancer who had undergone LEEP or cone biopsy before radical hysterectomy. Surgicopathologic features of LEEP and cone biopsy specimens were correlated with the presence or absence of residual tumor in radical hysterectomy specimens.

Results—Forty-two patients met the inclusion criteria. At radical hysterectomy, 22 patients (52%) had no residual tumor, while 20 patients (48%) had residual disease. Margin status was the only statistically significant predictor of the presence or absence of residual disease at radical hysterectomy; positive margins predicted the presence of residual disease ($P < 0.001$).

Conclusion—Women with stage IA2 cervical cancer and negative margins on LEEP or cone biopsy specimens should be counseled that they may be at low risk for having residual disease in the final radical hysterectomy specimen.

Keywords

cervical cancer; conization; residual disease

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

INTRODUCTION

Among women worldwide, cervical cancer is the most common cause of cancer death and years of life lost [1]. Patients with stage IA1 cervical cancer (depth of invasion ≤ 3 mm, no visible lesion) are usually treated with simple hysterectomy or conization [2], but patients with stage IA2 disease (depth of invasion > 3 mm and < 5 mm and width of lesion < 7 mm, no visible lesion) have historically been treated with radical hysterectomy and pelvic lymphadenectomy [3]. Pelvic lymphadenectomy is an important part of treatment since up to 4% of patients with stage IA2 disease have nodal metastasis [4]. Unfortunately, radical hysterectomy can be associated with significant perioperative morbidity, such as urinary and rectal dysfunction, ureteral and vesical fistulas, intraoperative bleeding, infections, lymphedema, and pulmonary embolism [5].

In the United States, almost half of women diagnosed with cervical cancer are under the age of 35 years [6]. In younger women diagnosed with cervical carcinoma, the desire to maintain fertility without compromising long-term survival is an important issue. As more knowledge is gained regarding the pathogenesis of cervical cancer, conservative treatment of early-stage cervical carcinoma has been proposed as a reasonable option. Studies of conservative treatment for patients diagnosed with adenocarcinoma in situ of the cervix have suggested that cone biopsy alone may be appropriate for patients in whom a negative margin is obtained in the cone biopsy [7, 8]. Other investigators have proposed conservative treatment of patients with stage IA1 cervical cancer with conization alone to preserve fertility [9]. However, limited data are available regarding conservative therapy for patients with stage IA2 cervical cancer who may desire to maintain fertility. Fertility-sparing procedures for such patients may include radical trachelectomy combined with lymphadenectomy [10] or simple trachelectomy or cold knife conization combined with lymphadenectomy [9].

One of the most important steps that must be completed before conservative therapy can be implemented is to identify which patients are candidates for less radical treatment options. The goal of this study was to correlate findings on pathologic examination of loop electroexcisional procedure (LEEP) or conization specimens with residual disease in radical hysterectomy specimens in patients with stage IA2 cervical cancer to determine if a subset of such patients may be candidates for conservative, fertility-sparing treatment.

MATERIALS AND METHODS

After obtaining approval from the institutional review board of The University of Texas M. D. Anderson Cancer Center, which waived the requirement for informed consent, we used our departmental radical hysterectomy database to identify patients who were diagnosed with stage IA2 squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix by LEEP or conization between October 1990 and December 2006 and who underwent a radical hysterectomy at our institution. Patients were excluded if they did not have squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma or if they had disease stage other than IA2. Demographic and surgicopathologic data were retrospectively reviewed. Residual disease was defined as any evidence of tumor in the hysterectomy

specimen. Findings on pathologic examination of LEEP or conization specimens were then correlated with the presence or absence of residual disease in radical hysterectomy specimens.

For all patients, disease was staged using the International Federation of Gynecology and Obstetrics staging system for cervical cancer [3]. Prior to surgical treatment, pathologists specializing in gynecologic malignancies at M. D. Anderson Cancer Center reviewed all outside diagnostic pathology slides, including slides from LEEP or conization biopsy performed prior to presentation to our institution. Patients presenting to M. D. Anderson with early-stage cervical carcinoma routinely undergo a pretreatment staging evaluation that includes a complete physical examination and chest radiography.

Factors analyzed included patient age, endocervical curettage (ECC) results, and findings on pathologic examination of LEEP or cone biopsy specimens, including histologic subtype, depth of invasion, presence or absence of lymph-vascular space invasion (LVSI), tumor grade, and margin status.

Data were entered into a computerized database, and statistical analysis was performed using Fisher's exact test and the Pearson chi-square test to compare the proportions between groups. Statistical significance was defined as $P < 0.05$. Parametric continuous variables were compared using Student's t -test for independent samples. Nonparametric continuous and dichotomous variable comparisons were performed using the Mann-Whitney U test and the χ^2 test, respectively. Two-sided p values are reported. A p -value of less than 0.05 was considered to indicate statistical significance. SPSS 15 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

We identified 42 patients who met the inclusion criteria. The median age for the entire cohort was 37.6 years (range, 24.3-64.9). The median depth of invasion was 4.0 mm (range, 3.0-5.0). On final pathologic examination of radical hysterectomy specimens, 22 patients (52%) had no residual cancer, while 20 patients (48%) had residual disease. There was no statistically significant relationship between histologic subtype, depth of invasion, LVSI, ECC results, or tumor grade and the presence or absence of residual disease in radical hysterectomy specimens (Table 1).

Margin status was known for 35 (83%) of the 42 patients in the cohort. Of the 17 patients with known margin status and positive residual disease in the radical hysterectomy specimen, none had negative margins on the LEEP or cone biopsy specimen (Table 2). Positive margins were the only statistically significant predictor of residual disease at radical hysterectomy ($P < 0.001$; 95% CI: 0-31%).

For LEEP or cone biopsy margin status as a predictor of residual disease in the radical hysterectomy specimen, the sensitivity was 0.94, the specificity was 0.56, and the negative predictive value was 0.91. In the entire cohort of 42 patients, one patient—a patient without residual disease in the hysterectomy specimen but with LVSI on her LEEP biopsy specimen

— was found to have metastatic adenocarcinoma in one of two parametrial lymph nodes on lymphadenectomy.

DISCUSSION

Although radical hysterectomy is the current recommended treatment for patients with stage IA2 cervical cancer, our findings suggest the possibility of more conservative therapy for patients with stage IA2 disease and negative margins on LEEP or cone biopsy specimens. Of all the preoperative pathologic findings that we examined in this study, only positive LEEP or cone biopsy margins were predictive of residual disease at radical hysterectomy. Thus, in young women with stage IA2 cervical cancer with negative margins on LEEP or cone biopsy specimens, there may be a role for fertility-sparing procedures such as simple trachelectomy with laparoscopic lymphadenectomy or repeat conization with laparoscopic lymphadenectomy.

Radical trachelectomy (abdominal, vaginal, or laparoscopic), cold knife conization, or even observation has been considered for selected patients with early-stage cervical cancer who wish to preserve their fertility. Koliopoulos et al [11] recently published data on the role of conservative procedures in the treatment of stage IA2 cervical carcinoma. They concluded that radical vaginal trachelectomy should be the fertility-sparing procedure considered for women with stage IA2 cervical who wish to maintain fertility. Women who have undergone this procedure have been shown to have favorable pregnancy outcomes [12].

One patient in our series had metastasis to the lymph nodes. Although she did not have residual disease in the uterus and cervix, the preoperative LEEP specimen did have LVSI. Previous studies have demonstrated an increased risk for nodal metastasis in patients with LVSI detected on either preoperative pathologic examination of biopsy specimens [13] or postoperative pathologic examination of hysterectomy specimens [13,14]. In a study by Milam et al [13], the authors found that patients with preoperative LVSI in the cone biopsy specimen and depth of invasion > 4 mm were 6.6 times more likely to have lymph node involvement at the time of radical hysterectomy. Patients who have negative margins on LEEP or cone biopsy but who have LVSI may require nodal dissection with laparoscopic lymphadenectomy prior to consideration of fertility-sparing surgery.

An additional factor needs to be considered in determining whether patients with stage IA2 cervical cancer are candidates for fertility-sparing surgery—the likelihood of parametrial involvement. Parametrial involvement has been proven to be directly correlated with histologic subtype, tumor grade, depth of invasion, presence of LVSI, tumor size, lymph node metastases, and stage [15]. Parametrial involvement is associated with a 22% risk of recurrence, whereas absence of parametrial involvement is associated with only a 5% risk of recurrence [15]. Multiple investigators have successfully identified a subgroup of women with invasive cervical cancer who are at low risk for parametrial involvement in radical hysterectomy specimens. Wright et al [15] concluded that the recurrence rate after radical hysterectomy was 0.7% in women with tumors < 2 cm in diameter, negative pelvic lymph nodes, and no LVSI. The rate of parametrial spread in these patients was 0.4%. A similar study by Covens et al [16] showed a low incidence of parametrial involvement (0.6%) in

patients with tumors < 2 cm, negative pelvic lymph nodes, and depth of invasion < 10 mm. These studies support the concept that less invasive, fertility-sparing procedures may be appropriate for the patients with stage IA2 cervical cancer with appropriate preoperative characteristics.

In summary, in carefully selected women diagnosed with stage IA2 cervical cancer that have not completed childbearing, fertility-sparing procedures such as simple trachelectomy with laparoscopic pelvic lymphadenectomy or reconization with laparoscopic pelvic lymphadenectomy may be reasonable. These findings need to be confirmed in a large, multicenter study to evaluate the preoperative factors of patients with stage IA2 cervical carcinoma.

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Précis

Women with stage IA2 cervical cancer and negative margins on loop electroexcisional procedure or cone biopsy specimen are at low risk for residual disease at radical hysterectomy.

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Table 1

Association between findings on pathologic examination of LEEP or cone biopsy specimens and presence or absence of residual disease at radical hysterectomy*

Factor	No residual disease (n = 22)	Residual disease (n = 20)	P value
Histology			0.74
Squamous	13 (59)	14 (70)	
Adenocarcinoma	7 (32)	5 (25)	
Adenosquamous	2 (9)	1 (5)	
Depth of invasion			0.15
> 4.0 mm	3 (14)	7 (35)	
4.0 mm	19 (86)	13 (65)	
LVSI present	12 (55)	5 (25)	0.07
Positive ECC results	7 (32)	11 (55)	0.66
Positive nodes	1 (4)	0 (0)	1.0
Grade			0.95
1	3 (14)	3 (15)	
2	8 (36)	10 (50)	
3	6 (27)	6 (30)	
LEEP/cone biopsy margin status			<0.001
Positive	8 (36)	16 (80)	
Negative	10 (45)	1 (5)	
Unknown	4 (19)	3 (15)	

LVSI – lymph-vascular space invasion; ECC – endocervical curettage; LEEP – loop electroexcisional procedure.

* Values in table are numbers (percentages) of patients.

Table 2

Association between margin status and residual disease

Margin status	Residual disease at radical hysterectomy	
	Present	Absent
Positive	17	8
Negative	0	10

Sensitivity: $17/17 = 1.00$.Specificity: $10/18 = 0.56$.Negative predictive value: $10/10 = 1.00$.

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